"Not so immediate" hypersensitivity—the danger of biphasic anaphylactic reactions

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Abstract

***Objective*—To assess how commonly clinically significant biphasic anaphylactic reactions occur after apparently successful treatment of an anaphylactic reaction. Cases were analysed to determine whether there were any markers that would allow early identification of patients who would subsequently develop a biphasic response.**

***Method*—Retrospective review of case notes of 34 patients admitted for observation after an anaphylactic reaction that had required treatment with adrenaline.**

***Results*—Six patients (18%) had biphasic reactions. No clinical features on initial presentation identified those likely to have a biphasic response. These patients however required significantly more adrenaline to ameliorate their initial symptoms ($p = 0.03$) compared with those having a simple uniphasic reaction.**

***Conclusions*—Biphasic anaphylactic reactions occur frequently. There are no clinical features that allow identification of patients likely to have a biphasic response. These patients require higher doses of adrenaline to control their initial symptoms and this should be considered a marker for patients who may develop a biphasic response. These results confirm that all patients being discharged after treatment for an acute anaphylactic reaction must be made aware of the risk of a second phase response after apparent clinical resolution.**

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Anaphylactic reactions vary from mild to potentially life threatening episodes that may involve the respiratory, cardiovascular, gastrointestinal, and central nervous systems. The initial emergency management of severe acute anaphylactic reactions is agreed with adrenaline being the most important first line agent.[1–3] Other agreed first line treatments include oxygenation, removal of the offending substance (for example bee sting), and fluid resuscitation if required. Antihistamines and steroids have a supportive role in ongoing management.[1 4 5]

Most cases respond promptly to initial management, while some reactions are prolonged and last 24 hours or more despite medical treatment. In other cases symptoms and signs resolve only to return later, occasionally with fatal consequences.[6–8] The frequency of these biphasic anaphylactic reactions is often underestimated by primary care and accident and emergency (A&E) doctors. There are no reliable indicators in the literature that identify patients likely to develop a biphasic response.

The aims of our study were to assess whether biphasic anaphylactic reactions could be identified, whether they were clinically significant, and whether there were any features which would aid initial identification of patients likely to have a biphasic response.

Methods

Patients admitted to the short stay ward of a medium sized A&E department over a 18 month period with a diagnosis of anaphylaxis that had required treatment with adrenaline were identified. Anaphylaxis was defined as the occurrence of one or more of the following: generalised urticaria, upper or lower airway respiratory symptoms, gastrointestinal, central nervous system, or cardiovascular symptoms that occurred after antigen exposure.[6 9 10] Cases were then analysed to identify biphasic reactions. This was considered to have occurred where the patient had improved completely after initial treatment only to develop further symptoms requiring adrenaline. Adrenaline was administered by the intramuscular or subcutaneous route at conventional doses and intervals until resolution of symptoms.[3 4 9 11] All patients received adjunctive treatment with regular oral antihistamine and intravenous hydrocortisone.

Table 1 Causal antigen in 28 uniphasic and six biphasic reactions

	Uniphasic (n=28)	*Biphasic (n=6)*
Insect bites/stings	9	3
Nuts	5	1
Penicillin	2	1
Cephalosporin	1	—
NSAID	1	1
Shellfish	1	—
Unknown	9	—

NSAID = non-steroidal anti-inflammatory drug.

Table 2 Clinical features of anaphylaxis in uniphasic patient group (n=28)

Feature	*No of patients*
Objective features	
Rash	19
Facial oedema	10
Laryngeal/pharyngeal oedema	9
Peripheral oedema	6
Bronchospasm	3
Gastrointestinal	3
Hypotension	1
Subjective features	
Giddy, faint, flushed	8
Dyspnoea	7
Pruritis	3
Throat tightness	2
Chest tightness	1
Palpitations	1

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Table 3 Patients with biphasic response (n=6)

Patient No	*Initial features*	*Adrenaline for initial symptoms (mg)*	*Biphasic features*	*Adrenaline for second stage features (mg)*	*Time to secondary features (hours)*
1	Rash, nausea, lower RT	1.4	Rash/pruritis, dyspnoea, diarrhoea	0.4	18.25
2	Rash, upper RT	1.3	Rash, lower RT, periorbital oedema	0.6	23.75
3	Hypotension, cyanosis, vomiting, rash	2.0	Rash, peripheral oedema	1.0	29.50
4	Rash, pruritis	1.5	Rash, dyspnoea	0.4	4.50
5	Rash, dysphagia	0.5	Rash, pruritis, hypotension	0.5	9.00
6	Rash, pruritis, dysphagia	0.5	Rash, dysphagia	0.5	12.50

RT = respiratory tract.

We compared the patients who went on to develop a second reaction with those who did not, with respect to various clinical features and treatment of the first reaction. The χ^2 test and Mann-Whitney tests were used, and the 95% confidence interval was calculated for the difference in initial adrenaline doses.

Results

Thirty four patients with a diagnosis of anaphylaxis serious enough to require treatment with adrenaline were identified. There were 19 male and 15 female patients. The age range of subjects was between 16 and 81 years. There were no deaths. Causal antigens are shown in table 1.

The presenting features of uniphasic anaphylactic reactions are shown in table 2.

Eighteen per cent of patients (6/34) had a biphasic reaction. The initial presenting features were similar to those of the uniphasic group. None of these cases involved repeated exposure to the causal agent. The interval until development of the second stage of the biphasic response ranged from 4.50 to 29.50 hours. The symptoms exhibited in the second stage were similar to those of the initial presentation (table 3).

Patients with a uniphasic reaction required from 0.3 to 1 mg adrenaline (mean 0.6 mg) to treat symptoms. Patients with a biphasic reaction required 0.5 to 2.0 mg adrenaline to control symptoms at initial presentation (mean 1.2 mg). This difference was statistically significant ($p = 0.03$, 95% confidence interval 0 to 1 mg). The dose of adrenaline required to treat second stage features of biphasic reactions varied between 0.4 to 1.0 mg (mean 0.5 mg).

Discussion

The potential for the return of severe symptoms in someone who appears to have been successfully treated for an acute anaphylactic reaction is often underestimated. Biphasic reactions occurred in 18% of cases in this study with the second phase response developing more then 29 hours after the first in one patient (see table 3, patient 3). This incidence is similar to that previously reported by Sampson and Mendelson (23%)[8] but is considerably greater than that reported by Douglas *et al* (5% for inpatients and 7% for outpatients).[7] Our study confirms that there were no presenting clinical features that predicted a biphasic response. It has been suggested that those who ingest the antigen are at higher risk of developing a biphasic response.[6] This would only have identified half of our cases and we do not thus consider it a reliable indicator.

Our study identified that those who went on to develop a biphasic response required significantly more adrenaline to treat their initial reaction, although the number of patients in the study was small. We are not aware of previous similar reports in the literature. This would suggest that patients who require higher doses of adrenaline to treat anaphylaxis are at greater risk of a subsequent biphasic reaction. We are planning a prospective study with a larger group of patients to test this hypothesis.

All patients requiring adrenaline to control an anaphylactic reaction should be admitted for observation for at least 24 hours. Patients should only be discharged after being educated in the recognition and treatment of anaphylaxis.

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